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HLA-Cw4 in Paranoid Schizophrenia

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Recent papers agree that the distribution of HLA antigens in paranoid schizophrenia (SCH) is not normal although the detailed data are not uniform and do not point to a conclusive increase of a certain HLA antigen.

Eberhard et al. (1975) found a significant increase of HLA-A9 in 43 chronic paranoid SCH patients; indications were also given for increased frequency of Aw19 and B5 in the younger group of patients. Iványi et al. (1976) found a significant increase of HLA-A28 and indications were found for an increased frequency of haplotype A10, B18 in a group of 148 SCH patients (80% of the paranoid subtype). The support for an association of HLA-A9 with the paranoid subtype of SCH is also found in the study of Cazzullo et al. (1974). Bennahaum et al. (1976) report no increase of either A9 or A28 (Bw17 was increased). Mercier et al. (1976) found increased frequency of A9 and B5. The associations found in the last three papers

mentioned were not significant after correction of P values and were obtained on relatively small series of 15-20 SCH patients. Patients of Swedish (43), Italian (20), USA-Spanish (16), USA-Anglo (20), French (15) and Czech (148) origin were tested in these studies.

In this communication we present data which could bring the above mentioned diverse findings to a common denominator.

In continuation of our previous study a further 40 patients with paranoid SCH were HLA serotyped. The origin of patients, criteria of diagnosis, age distribution as well as the serological methods were the same as described in our previous study (Iványi et al. 1976). Only male patients were tested. In addition to antigens of the HLA-A and HLA-B series the serotyping was completed by typing of HLA-C series antigens (CW1-Cw5). Each antigen was determined by 2-4 mono- or oligospecific sera.

The results are summarized in Table 1. It

Table 1
HLA antigens of A, B and C series in paranoid schizophrenics

Antigens	Frequency (%) in		chi ²	R.r.
	controls (N = 1200) ^a	patients (N = 40)		
A1	27.58	15.0	3.10	0.46
A2	48.83	57.5	1.16	1.42
A3	26.83	20.0	0.92	0.68
A9	22.83	37.5	4.66	1.97
A10	16.33	25.0	2.10	1.71
A11	11.16	12.5	0.07	1.14
A28	6.33	10.0	0.86	1.65
Aw19	8.91	12.5	0.60	1.46
B5	12.00	17.5	1.09	1.56
B7	23.25	10.0	3.86	0.36
B8	17.41	17.5	0.01	1.01
B12	22.00	35.0	3.76	1.91
B13	9.00	7.5	0.11	0.82
B14	3.00	0.0	1.23	0
B18	11.06	30.0	13.41*	3.47
B27	9.58	15.0	1.29	1.66
Bw15	10.91	12.5	0.10	1.17
Bw16	10.13	2.5	2.55	0.23
Bw17	6.33	2.5	0.98	0.30
Bw21	2.91	0.0	1.20	0
Bw22	3.66	5.0	0.19	1.37
Bw35	16.25	20.0	0.40	1.28
Bw40	9.91	10.0	0.01	1.01
Cw1	6.30	5.0	0.12	0.78
Cw2	10.30	15.0	0.90	1.54
Cw3	15.70	5.0	3.39	0.28
Cw4	15.31	40.0	17.40**	3.69
Cw5	9.85	0.0	4.35	0

^a For C series antigens only 438 individuals tested

* P corrected < 0.05

** P corrected < 0.01

Relative risk (R.r.) of schizophrenia for Cw4 is 3.69 with 95% confidence limits 1.86 — 7.30.

can be seen that both A9 and A28 antigens are slightly, but not significantly increased. The same holds for A10 and B18, in support of our previous observation (Iványi et al. 1976).

A highly significant increase was obtained for Cw4 antigen ($\chi^2 = 17.4$, $P_c < 0.01$, relative risk is 3.69 with 95% confidence limits 1.86 — 7.30). The occurrence of Cw4 was connected neither with the age of patients at the onset of disease nor with

the age at the time of testing and the duration of the disease.

The following explanation seems to fit well with both previous and present data on association of HLA antigens with paranoid SCH. We suggest that all these diverse data may be explained by the association of the antigens involved with Cw4. Antigen Cw4 is known to be most frequently associated with antigen Bw35. Antigen Bw35 is frequently on haplotypes

bearing A9 holds for the and B12. Bo increased in patients. Ma population v 184 HLA h studies) only four of them ported. The with A9 (or and A9, Cw 1975, Nielse (1975) rema more freque carrying A9 B12 without A9 (w23), C pronounced ation betwe than expecte between ther

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bearing A9 or A28. The same argument holds for the gametic association of Cw4 and B12. Both Bw35 and B12 are slightly increased in the present series of paranoid patients. Mayr (1975) has shown (on a population very close to ours) that from 184 HLA haplotypes (defined by family studies) only nine contained A28 and in four of them A28, Cw4, Bw35 was incorporated. The frequent association of Cw4 with A9 (on haplotypes A9, Cw4, B12 and A9, Cw4, Bw35) was indicated (Mayr 1975, Nielsen et al. 1975). Nielsen et al. (1975) remark that Cw4 is significantly more frequent on B12 haplotypes also carrying A9 than on haplotypes carrying B12 without A9. The "superhaplotype" A9 (w23), Cw4, B12, serves as the most pronounced example in which the association between three factors is stronger than expected from the pairwise association between them (Nielsen et al. 1975).

The possible mechanism which might be involved in HLA and disease associations has been reviewed by several authorities, more recently by Svejgaard (1976). For the HLA and SCH association, from the broad field of possibilities, two seem to be the most plausible (however others must not be excluded). First, the involvement of "non-immunological" ligand receptor interaction, as hypothesized by Svejgaard (1976) and supported by numerous data from the mouse H-2 model (Iványi 1975). Second, the involvement of a virus susceptibility locus in accordance with the reasoning of Nyulassy et al. (1975, 1976) in connection with a viral disease strongly associated with Bw35. The present paper supports the possibility that associations based on these mechanisms are due to gene(s) located in the HLA central part analogous to some similar functions located in the H-2 central part.

Summary

On a group of 40 paranoid schizophrenic patients HLA serotyped for HLA-A, B, C antigens a significant increase of Cw4 was observed. It is argued that this finding represents the common denominator for previous data reporting increased A9 and A28 antigens in SCH because these antigens are frequently present on haplotypes bearing Cw4. The possible role of the HLA "central" parts, i.e. the chromosomal segment between HLA-A and HLA-B locus in the pathogenesis of schizophrenia was stressed.

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